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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/698,070	10/30/2003	Frederic J. Kaye	221749	1623
45733 7590 11/07/2007 LEYDIG, VOIT & MAYER, LTD. TWO PRUDENTIAL PLAZA, SUITE 4900 180 NORTH STETSON AVENUE CHICAGO, IL 60601-6731			EXAMINER VIVLEMORE, TRACY ANN	
			ART UNIT 1635	PAPER NUMBER
			MAIL DATE 11/07/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/698,070

Applicant(s)

KAYE ET AL.

Examiner

Tracy Vivlemore

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 August 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3-26,35-43 and 45-66 is/are pending in the application.
- 4a) Of the above claim(s) 7,17 and 47-62 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3-5,8-15,18-26,35-43,45,46 and 63-66 is/are rejected.
- 7) ☒ Claim(s) 6 and 16 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection not reiterated in this Action is withdrawn.

Claim Rejections - 35 USC § 103

Claims 1, 4, 5, 8-10, 12, 13, 18-21, 23-26, 36, 38-41, 43, 45, 46 and 63-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al. (Molecular and Cellular Biology 2002, of record) in view of Bass (Nature 2001, of record) and Bhanot (US 2004/0006005, of record).

The claims are directed to compositions for inhibition of a gene that consist essentially of a fragment of the nucleotide encoding a Mect1-MAML2 chimeric gene and a nucleic acid complementary to the fragment wherein the fragment is 17-32 nucleotides in length. In specific embodiments the chimeric gene has the sequence shown in SEQ ID NO: 1 and results from a t(11;19) translocation. In other embodiments the composition is in a plasmid or viral vector that may comprise two different promoters such as RNA polymerase promoters, the fragment of the gene is of varying lengths and the composition contains 3' overhangs of 1-4 nucleotides that may be uridines. Other embodiments recite that the composition has the function of inhibiting growth of a cancer cell comprising a Mect1-MAML2 chimeric gene and that this inhibition is at least about 50%.

Wu et al. teach the characterization of two genes that are mammalian homologues of the Mastermind gene of *Drosophila*, MAML2 and MAML3. The

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sequence of MAML2 is found in Genbank accession number XM_045716. Wu et al. teach that these genes are widely expressed in adult tissues but exhibit distinct expression patterns in mouse early spinal cord development, indicating that MAML proteins may modify Notch signaling in different cell types and contribute to the diversity of biological effects that result from Notch activation based on their own expression levels and differential activities (see abstract). Wu et al. do not teach siRNAs targeted to MAML2.

Bass teaches on page 429, first column, that RNA interference is a routinely used gene silencing technique that has proven to be more robust than antisense techniques by working more often, decreasing expression to lower levels than antisense oligonucleotides and working at concentrations several orders of magnitude below the concentrations typically used in antisense experiments. Bass further teaches in the same column that the discovery of short interfering RNAs that are functional in mammalian cells will inspire further research studies aimed at optimizing the use of siRNAs, as well as at understanding why conventional RNAi using longer dsRNA works in eggs and embryos. Bass speculates that, based on the huge impact the RNAi technique has had in studies of non-mammalian systems, use of siRNA in mammalian cells could be just as far-reaching, with applications extending to functional genomics and therapeutics.

Bhanot teaches at paragraph 12 that preferred target regions for expression inhibitors such as siRNAs include the coding region and the stop codon region, defined in paragraph 31 as a portion of a gene encompassing from about 25 to about 50 contiguous nucleotides in either direction from a translation termination codon. Bhanot

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incorporates by reference at paragraph 27 the teachings of other artisans regarding siRNA and vector design including teaching that vectors can be plasmids or viral vectors (found in WO 01/36646), vectors can comprise two RNA strands under control of different RNA polymerase promoters (found in WO 99/32619) and that siRNAs can comprise 3' overhangs that comprise uridine (found in Elbashir et al, EMBO Journal). Based on this, Bhanot teaches that design of a siRNA or a vector coding for the siRNA to inhibit a nucleotide sequence is well within the skill of the ordinary artisan.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to target MAML2 with siRNAs for the purpose of studying gene function as taught by Bass and to make the siRNA targeted to the stop codon region as taught by Bhanot. Wu et al. provide a motivation to target MAML2 in order to study its function by teaching that MAML2 is involved in Notch signaling and contributes to the diverse biological effects that result from Notch activation. Bass provides a motivation to make siRNAs to a gene of interest by teaching they are more effective than antisense oligonucleotides and that the use of siRNAs is poised to have a huge impact on studies of mammalian systems such as study of gene function. Bhanot provides a motivation to make a siRNA targeted to the stop codon region of MAML2 by teaching that it is a preferred target region for inhibitory nucleic acids. One of ordinary skill in the art would have had a reasonable expectation of success in making siRNAs to MAML2 because the sequence of MAML2 is known and Bhanot teaches that design of siRNAs to target a gene is readily accomplished by those in the art. Because the chimeric gene that encodes SEQ ID NO: 12 comprises MAML2 and in particular comprises the stop codon region of this gene, any siRNA targeted to this region of MAML2 will necessarily

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comprise a fragment of a nucleic acid encoding SEQ ID NO: 12 and a nucleic acid complementary to this fragment and will, absent evidence to the contrary, inhibit the translation of a MECT1-MAML2 gene and inhibit growth of cancer cells comprising this fusion gene.

Thus, the invention of claims 1, 4, 5, 8-10, 12, 13, 18-21, 23-26, 36, 38-41, 43, 45, 46 and 63-66 would have been obvious, as a whole, at the time the invention was made.

Claims 1, 4, 5, 8-13, 18-26, 36, 38-41, 43, 45, 46 and 63-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al., Bass and Bhanot as applied to claims 1, 4, 5, 8-10, 12, 13, 18-21, 23-26, 36, 38-41, 43, 45, 46 and 63-66 above, and further in view of Nicklin et al. (Current Gene Therapy 2002, of record) and Sui et al. (PNAS 2002, of record).

Claims 1, 4, 5, 8-10, 12, 13, 18-21, 23-26, 36, 38-41, 43, 45, 46 and 63-66 are described in the previous rejection over Wu et al., Bass and Bhanot. Claim 11 recites a viral vector that is an adenoviral vector. Claim 22 recites RNA polymerase III (Pol III) promoters.

The teachings of Wu et al., Bass and Bhanot are described in the previous 103 rejection. Wu et al., Bass and Bhanot do not teach compositions in an adenoviral vector or use of Pol III promoters.

Nicklin et al. teach that replication defective adenoviral vectors have been successfully used for gene delivery in many applications.

Sui et al. teach DNA vectors for producing siRNA molecules suitable for use in RNA interference. These vectors are plasmids that operate under control of the U6 promoter, which is a Pol III promoter.

The teachings of Wu et al., Bass and Bhanot are obvious for the reasons described in the previous 103 rejection. It would have been further obvious to use an adenoviral vector or a vector that comprises a Pol III promoter. Sui et al. provide a motivation and reasonable expectation of success in using vectors comprising Pol III promoters by teaching their successful use to produce siRNAs that reduce gene expression. Nicklin et al. provide a motivation and expectation of success in using an adenoviral vector by teaching that adenoviral vectors are widely used as gene delivery systems.

Thus, the invention of claims 1, 4, 5, 8-13, 18-26, 36, 38-41, 43, 45, 46 and 63-66 would have been obvious, as a whole, at the time of invention.

Claims 1, 4, 5, 8-10, 12, 13, 15, 18-21, 23-26, 36-41, 43, 45, 46 and 63-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al., Bass and Bhanot as applied to claims 1, 4, 5, 8-10, 12, 13, 18-21, 23-26, 36, 38-41, 43, 45, 46 and 63-66 above, and further in view of Parrish et al. (Molecular Cell 2000, of record)

Claim 1, 4, 5, 8-10, 12, 13, 18-21, 23-26, 36, 38-41, 43, 45, 46 and 63-66 are described in the 103 rejection under Wu et al., Bass and Bhanot. Claims 15 and 37 recite the complementary nucleic acid can contain up to 3 base substitutions.

The teachings of Wu et al., Bass and Bhanot are described in the 103 rejection over these references. They do not teach siRNAs comprising base substitutions, but

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Parrish et al. teach that base substitutions commonly used in nucleic acid therapeutics are tolerated in the double stranded RNAs used for RNA interference.

The teachings of Wu et al., Bass and Bhanot are obvious for the reasons described above. It would have been further obvious to one of ordinary skill in the art at the time of invention to make siRNAs containing base substitutions. Parrish provides a motivation and reasonable expectation of success in using base substitutions, teaching that base modifications known in the art of nucleic acid therapeutics to impart increased stability are tolerated in the double stranded RNA used in RNA interference.

Thus, the invention of claims 1, 4, 5, 8-10, 12, 13, 15, 18-21, 23-26, 36-41, 43, 45, 46 and 63-66 would have been obvious, as a whole, at the time of invention.

Claims 1, 3-5, 8-10, 12-14, 18-21, 23-26, 35, 36, 38-43, 45, 46 and 63-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al., Bass and Bhanot as applied to claims 1, 4, 5, 8-10, 12, 13, 18-21, 23-26, 36, 38-41, 43, 45, 46 and 63-66 above, and further in view of Beach et al. (US 2004/0086884, of record) and Taylor et al. (US 6,331,425, of record).

Claim 1, 4, 5, 8-10, 12, 13, 18-21, 23-26, 36, 38-41, 43, 45, 46 and 63-66 are described in the 103 rejection under Wu et al., Bass and Bhanot. Claims 3, 14, 35 and 42 recite the presence of a sequence recognized by a restriction enzyme that may be *Hin dIII* that joins the sequences of the composition.

The teachings of Wu et al., Bass and Bhanot are described in the 103 rejection over these references. They do not teach siRNAs comprising a hairpin loop that contains a restriction enzyme site, but Taylor et al. teach *Hin dIII* is one example of a

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restriction enzyme at column 3, first paragraph and Beach et al. specifically teach siRNA hairpin loops containing restriction sites in claim 53.

The teachings of Wu et al., Bass and Bhanot are obvious for the reasons described above. It would have been further obvious to one of ordinary skill in the art at the time of invention to incorporate a restriction site into a hairpin loop. Beach et al. provide a motivation and reasonable expectation of success by explicitly teaching siRNAs comprising such loops. Given the knowledge in the art that Hin dIII is a restriction enzyme as evidenced by Taylor et al., one of ordinary skill in the art would recognize the use of that particular enzyme to be mere design choice.

Thus, the invention of claims 1, 3-5, 8-10, 12-14 18-21, 23-26, 35, 36, 38-43, 45, 46 and 63-66 would have been obvious, as a whole, at the time of invention.

Response to Arguments

Applicants traverse the rejection by arguing the prior art does not suggest using siRNA to test the function of MAML2, noting that none of the references cited discloses siRNA molecules directed to MAML2. Applicants further note that at the time of filing a vast number of methods were available for this purpose, several of which were employed by Wu et al. Applicant is correct that no one reference alone discloses siRNAs directed to MAML2, however the present rejection is applied under 103, which necessarily combines the teachings more than one reference. Applicants conclude nothing in Wu et al. or any other reference cited suggests that siRNA would be more appropriate than other methods of studying gene function. While it may be true that several methods exist for testing gene function, the assertion that no reference

suggests siRNA is more appropriate is incorrect, Bass teaches that siRNAs have several advantages over the antisense oligonucleotides routinely used for studying gene function at the time that siRNAs were discovered.

Applicants additionally argue the combined disclosures of the cited references would not have led one of ordinary skill in the art to the claimed subject matter, noting that because the Mect1-MAML2 fusion gene comprises only part of MAML2 not every siRNA designed to inhibit MAML2 would inhibit the fusion gene. While it is correct that only a portion of MAML2 is present in the fusion gene, this point is specifically addressed in the rejection, which states that a siRNA targeted to the stop codon region of MAML2 would also target the Mect1-MAML2 fusion and would in the absence of evidence to the contrary inhibit the fusion gene.

Applicants further argue Bhanot does not suggest targeting the stop codon region over any other portion of an mRNA transcript and actually teaches that any portion of the mRNA may be targeted. Applicants further note that the working examples of Bhanot show that stop codon-targeted siRNAs are no more preferable than siRNAs directed to the start codon or coding sequences. This argument is not persuasive because an obviousness rejection does not require a teaching that siRNAs targeted to the stop codon region are more active than other siRNAs, there merely needs to be a suggestion to target this region. This reason is found in the Bhanot reference. While Bhanot suggests other regions may be targeted, this reference also explicitly suggests targeting the stop codon region of a gene.

Applicants further assert the portion of the instant specification disclosing the structure of the Mect1-MAML2 chimera has been used as prior art. This argument is not

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persuasive because the rejection is not based on the use of the specification as prior art; the rejection is based only on the Wu, Bass and Bhanot references. Applicants argue one of ordinary skill in the art at the time of filing would not have had the benefit of knowing that exons 2-5 of MAML2 were part of the Mect1-MAML2 fusion gene product and one applying siRNA to MAML2 would not necessarily be led to the claimed subject matter. While it may be correct that those in the art would not have had the benefit of knowing the structure of the Mect1-MAML2 fusion gene, the rejection is based on why it is obvious to one of ordinary skill in the art to make siRNAs targeted to MAML2. To the extent that siRNAs targeted to MAML2 will also bind to the fusion gene, these siRNAs meet the structural limitations of the claims and in the absence of evidence to the contrary possess the capability of inhibiting translation of a Mect1-MAML2 fusion gene and render obvious the claimed invention.

Allowable Subject Matter

Claims 6 and 16 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has

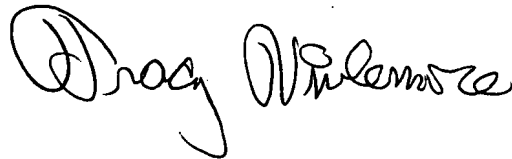
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been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see <http://pair-direct.uspto.gov>.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore
Examiner
Art Unit 1635

TV
November 6, 2007

A handwritten signature in black ink, appearing to read "Tracy Vivlemore", written in a cursive style.